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The paradox of using a 7 day antibacterial course to treat urinary tract infections in the community

R. CHEUNG[1], C. M. SULLENS[1], D. SEAL[3], J. DICKINS[2], P. W. NICHOLSON[4], A. A. DESHMUKH[5], M. J. DENHAM[1] & S. M. DOBBS[1]

[1]Therapeutics in the Elderly, Research Group, [2]Department of Bioengineering and the [3]Division of Communicable Diseases, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ, [4]The University College and Middlesex School of Medicine, London W1P 6DB and [5]the School of Pharmacy, Brunswick Square, London WC1 1AX.

1 We have studied determinants of outcome of 7 day courses of treatment in 77 middle aged and elderly patients, in whom the general practitioner's diagnosis of urinary tract infections had been confirmed microbiologically. Bacteria were sensitive to cephalexin or trimethoprim. Where there was no preference, treatments were allocated randomly. Compliance was monitored using a pill box with a concealed electronic device which recorded openings of the box.

2 Prescribing trimethoprim, 200 mg twice daily, was more effective than cephalexin, 250 mg four times daily (cure rates 93 and 67%) ($P < 0.006$). Those cured and not cured were not distinguished by age, gender, genitourinary history, or infecting organism.

3 Compliance as measured by box openings was worse for cephalexin than for trimethopim ($P = 0.01$). However, both totality and pattern of compliance were similar in patients cured and not cured by cephalexin. Thus rigid adherence to a conventional course did not promote cure: fewer doses could have been prescribed.

4 Estimating compliance is essential to clinical trials where medication is self-administered. Poor compliance may establish over exacting regimens. Counting box openings did overestimate compliance, but counting residual tablets overestimated it grossly: given the number of openings less than the ideal, there should have been 171 residual tablets, only 55 were found.

Keywords compliance cure trimethoprim cephalexin

Introduction

A single large dose of the appropriate antimicrobial can be as effective in treating urinary tract infections as a conventional course, of lower doses, lasting several days (Stamm, 1983). Patients are likely to be motivated to take a single dose, which is prescribed at the time they seek advice. During the course of repeated medication, motivation may decline, or the patient may decide not to complete the course, on the one hand because symptoms have abated, or on the other because they persist. In order to monitor both totality and pattern of compliance with medication, we have developed a 'pill box' containing a concealed electronic device which records the times at which the box opened (Dickins *et al.*, 1986). This was used to study the effect of compliance with 7 day courses of antibacterial agents on outcome of treatment for urinary tract infections in 77 middle aged and elderly patients.

Correspondence: Dr S. M. Dobbs, Therapeutics in the Elderly, Research Group, Clinical Research Centre, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ

Methods

Patients in the community served by Northwick Park Hospital, aged 50 years and over, in whom a clinical diagnosis of urinary tract infection made by the general practitioner had been confirmed microbiologically, and with infections sensitive to cephalexin or trimethoprim, were eligible for entry into the study. The criteria for infection were greater than 10^8 colony forming units l^{-1} of a single organism and 50 or more pus cells/mm^3 in a mid stream specimen (MSU) of urine. Exclusions were made for the following reasons: antibacterial treatment had been started, there were symptoms (loin pain, rigors, pyrexia, nausea or vomiting) suggestive of pyelonephritis, there was a history of renal insufficiency, stones, or of major anatomical abnormality of the urinary tract, a urinary catheter was *in situ* or the patient was living in a residential home. Informed consent for monitoring the outcome of treatment was sought, but patients were not aware of the presence of the recording device in the pill box. They were, however, asked to evaluate the suitability of the pill box for use by the elderly or disabled. The study had the approval of the local ethics committee.

A brightly coloured plastic box (110 × 90 × 35 (height) mm) with a hinged lid (The Plastic Box Co. Ltd Lincolnshire, U.K.) and an inner container was used for the tablets (Figure 1). A portion of the roof of the inner container was cut away, sufficiently to allow easy removal of tablets by placing thumb and index finger inside or by tilting the box and decanting them; the remainder of the roof served to minimise spillage. Two bar magnets, one fixed to the lid, the other to the body of the box, provided a means of holding it closed, and protruding ledges on lid and body facilitated opening.

Figure 2 shows the electronic circuit of the recording device. Each time the pill box was opened, the counting system was triggered by a reed switch operated by the bar magnets. The number of openings in any hour was counted in an 'event counter'. At the end of the hour, a quartz controlled clock incremented the 'hours counter', transferred the count in the event counter to the memory, and set the event counter to zero in readiness for the next hour. The memory capacity was sufficient to store up to 15 events (openings) for each of 1024 hourly intervals (i.e. for 42 days). The design was implemented from CMOS integrated circuits and had a current consumption of less than 1μ Amp, thus allowing operation from a small inexpensive battery over the entire period. The information stored in the memory was accessed by attaching an external interface controlled by a microcomputer. A short computer program allowed the stored data to be read out and the memory to be reset, this being accomplished in less than 2

Figure 1 The pill boxes. The inner container has been removed from the box on the right to show the printed circuit board.

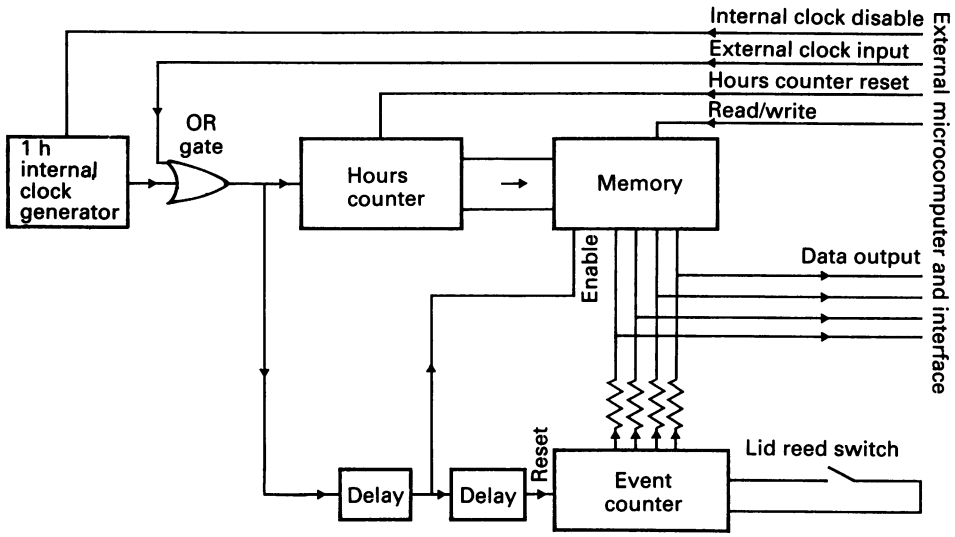

Figure 2 Block diagram of electronic circuit

min per box. For the purpose of the present study, no more than one event per hour was regarded as a representative of a dose of medication being removed from the box. Two events in adjacent memory locations were held to represent a single administration time which straddled a time change and the second event was thus ignored.

Antibacterial medication was dispensed in pill boxes, labelled clearly as to contents and treatment regimen and with the instruction on the inner container that the lid should be closed. Each box contained 28 tablets of cephalexin (Glaxo Laboratories Ltd), each 250 mg, one to be taken four times a day, or of trimethoprim (Norton and Co. Ltd) each 100 mg, two tablets to be taken twice a day. Which antibacterial the patient received was governed by any relevant history of allergy and the *in vitro* sensitivity of the organism (agar diffusion technique (Bauer *et al.*, 1966) using 1.25 μg trimethoprim and 30 μg cephalexin discs). Where there was no preference, a table of random numbers was used to allocate treatments. At the time of dispensing the tablets, the clinical pharmacist made an appointment to visit the patient's home 7 days later to collect the pill box, obtain a second MSU specimen and complete a questionnaire.

Cure was defined as the presence of fewer than 10^7 colony forming units l^{-1} of the same species, with the same *in vitro* sensitivities, as the initial organism. The third MSU specimen was obtained 1 week after the course should have finished in patients whose second specimen did not show persistence of the infection: most relapses occur within 1 week after the completion of therapy, whereas reinfections by the same organism, which has persisted in the stool, occur several weeks or months later (Fang *et al.*, 1979).

In the questionnaire patients were asked to compare the pill box with a standard, 'child proof', screw topped plastic bottle. Those found to have transferred tablets to a container other than the pill box were excluded. Any symptom which the patient suspected to be an adverse reaction to the antibacterial was noted as was the number of days for which symptoms referable to the urinary tract infection lasted after the tablets had been dispensed. Previous urinary tract disease and genitourinary operations were recorded. A drug history was taken, the number of dosage units per day (pills, sachets and spoonsful of medicine) prescribed on a regular basis being counted. Short term memory and calculation were tested: the patient was asked to repeat the address '74 Columbia Rd', memorise it and then recall it 5 min later and to subtract serial sevens from 100. When the pharmacist returned to the base hospital, the tablets remaining in the box were counted and the electronic recording device interrogated.

Results

Eighty patients entered the study. There were three drop outs: in one patient another antibacterial agent was substituted for trimethoprim

by the family practitioner prior to the first follow up visit because of 'persistent' urinary symptoms, the second transferred tablets intermittently to another container and the third vomited shortly after the first dose of trimethoprim and requested alternative medication.

Of the 77 patients to complete the study, 64 were female, 13 male, their mean (s.d.) age being 69(9) years, range 50 to 88 years. Seventy-four patients stated a preference with respect to tablet containers: 62 preferred the pill box to a standard screw topped plastic bottle and 12 held the opposite view. Only two patients attributed unwanted effects to the antibacterial treatment: both experienced nausea on trimethoprim. Symptoms referable to the urinary tract lasted for a mean of 3.2 (1.6) days. Fifteen patients had a previous history of urinary tract disease and 18 had had genitourinary operations. The mean number of dosage units (tablets, capsules, sachets and spoonsful) prescribed on a regular basis was 2.9(3.5) per day, range 0 to 14. The results of the cognitive function test were as follows: the mean score out of 4 for the short term memory test was 3.2(1.5) and out of 14 for calculation was 11(5).

The initial infecting organism was *Escherichia coli* in 64 patients, *Proteus spp.* in six, *Klebsiella spp.* in four and *Streptococcus faecalis, Staphylococcus aureus* and *epidermidis* each in one. Choice of therapy was made on the grounds of *in vitro* sensitivity testing in 49 patients: 31 received trimethoprim and 18 cephalexin. Thirteen patients were allocated randomly to receive trimethoprim, 15 to receive cephalexin.

The initial infection was cured in 63 of the 77 patients, but five had acquired a new infection by 1 week after the prescribed course should have been completed. Patients who were cured were not distinguished from those who were not by age (70) (9) and 69 (10) years, respectively (unpaired t-test, $t = 0.83$, $P > 0.4$), proportion of males (9/63 and 4/14, Fisher's exact test, $P = 0.24$), history of urinary tract disease (11/63 and 4/14, $P = 0.31$) or genitourinary operations (13/63 and 5/14, $P = 0.29$), or proportion of infections caused by *Escherichia coli* (53/63 and 11/14, $P = 0.49$). Prescribing trimethoprim in a dose of 200 mg twice daily for 7 days appeared to be more effective than cephalexin 250 mg four times a day for the same period, the cure rates being 41/44 (i.e. 93%) and 22/33 (67%) respectively ($P = 0.006$).

With respect to duration of treatment, a minimum of 6 days had elapsed between the first and last openings of the pill box by each of 72 patients, but ten of these were not cured. Of the remaining five patients, one who was given cephalexin, opened the box only four times, spread over 3 days, but he was cured. Three who were given trimethoprim, opened their boxes twelve times over 4 days, seven times over 3 days and twice in 1 day, respectively and were also cured, but one patient given trimethoprim, who only opened his box once, was not. Of the two patients who suffered nausea on trimethoprim, one was the patient who stopped treatment after 3 days, but the other apparently persisted with the course, opening the box 14 times in 8 days.

Figure 3 shows the distribution of the total number of box openings by each patient around the ideal. Compliance with the cephalexin regimen was significantly (Fisher's exact text, $P = 0.01$) worse than with the trimethoprim regimen: 20 of the 33 patients receiving cephalexin opened the box less than the ideal number of times, but only 13 of the 44 receiving trimethoprim defaulted in this way. Pill counting

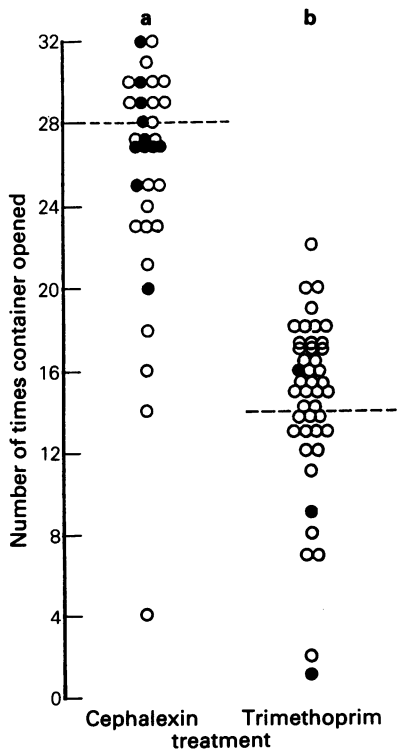

Figure 3 Number of times the pill box was opened by a) the 33 patients who received cephalexin and b) the 44 who received trimethoprim. The interrupted lines indicate the ideal number of openings for each antibacterial course. Open circles denote patients in whom the infection was cured, closed circles those in whom it was not.

gave gross overestimation of the number of compliant patients: only three of the patients given cephalexin and three given trimethoprim had residual tablets. Moreover, given the number of box opening less than the ideal, there should have been a total of 110 residual trimethoprim tablets and 61 of cephalexin, but only 41 trimethoprim and 14 cephalexin were found. However, the explanation for the high failure rate of treatment with cephalexin did not lie in the number of box openings: the proportion of patients who had opened the box less than the ideal number of times was similar in the patients who were cured, 13/22, and those who were not, 7/11 ($P = 0.74$).

Figure 4 shows the distribution of dosage intervals in those treated with cephalexin and trimethoprim. Only 7% of the dosage intervals on cephalexin met the ideal of 6 h, whilst 17% of those on trimethoprim met the ideal of 12 h. On cephalexin 59% of dose intervals were shorter than the ideal, the commonest interval being four hours, whilst 27% were between 8 and 16 h and usually occurred around night time. (Inspection of the cumulative plots of box openings against time of day for each patient prescribed cephalexin showed no evidence to suggest that the second and/or third dose of the day had been removed along with the first). On trimethoprim 67% of the intervals were between 8 and 16 h, the commonest being the ideal of 12 h. The distribution of intervals was similar in cured and uncured patients treated with cephalexin. An index of the consistency of dosage intervals, namely the proportion of the total number of intervals which were of 4, 5 or 6 h, was calculated

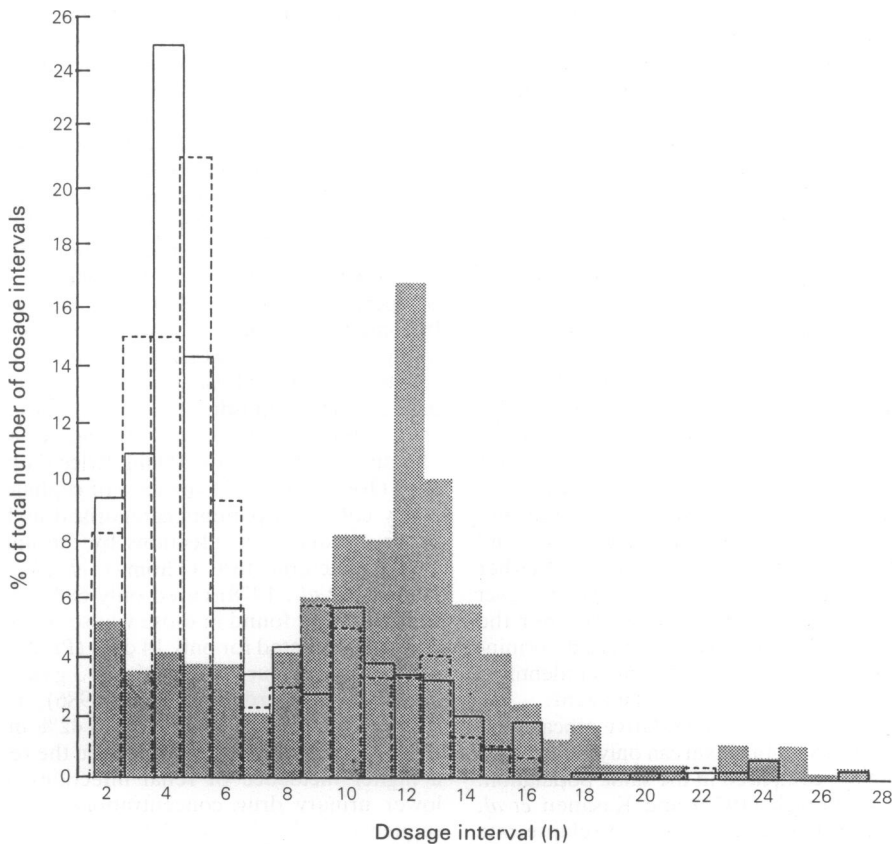

Figure 4 % of total number of intervals between pill box openings to fall within given time limits. The continuous line shows the distribution of intervals between openings of boxes containing cephalexin in the 23 patients in whom the infection was cured, the interrupted line that is 10 patients not cured by cephalexin. The shaded area shows the distribution of such intervals for 43 patients given trimethoprim. (One patient receiving trimethoprim was excluded because he opened the box only once). Since only three patients who received trimethoprim were not cured, the corresponding distributions for cured and uncured patients are not shown.

for each of the 31 patients who administered their own cephalexin. There was a significant correlation between the number of box openings and the consistency index (Spearman's rank correlation test, $r_s = 0.40$, $P < 0.025$), those with the smallest number of box openings having the lowest indices. However, in those who opened the box sufficient times to complete the course, the range of the consistency index was wide, 0.26 to 0.64. For trimethoprim, we took the consistency index to be the number of intervals of 11, 12 or 13 h. Its value ranged from 0 to 0.93. The relationship between the index and the number of openings did not reach significance at the 5% level ($P < 0.1$).

Age, gender, duration of symptoms referable to the urinary tract, number of dosage units of concurrent medication, short term memory and ability to calculate were not related to total number of openings of boxes containing either cephalexin or trimethoprim, or to the corresponding consistency index ($P > 0.05$ in each case, Mann-Whitney U test in the case of gender, otherwise Spearman's rank correlation test).

Discussion

The chance of cure was not increased in those of our middle aged and elderly patients who appeared to adhere rigidly to a conventional course of antibacterial therapy. There was no evidence to support the popular belief that relapse is associated with unduly long intervals between doses during which drug concentrations in tissue and urine are low and residual organisms are able to multiply. Although the cure rate for cephalexin, the drug with the shorter half time, was significantly lower than for trimethoprim, the patterns of compliance of patients cured and uncured by cephalexin were similar. Neither age, gender, previous history or urinary tract disease or of genitourinary operation, nor the nature of the infecting organism were determinants of outcome. The only determinant identified was the nature of the antibacterial agent.

A realistic estimate of the relative efficacies of trimethoprim and cephalexin can only be obtained when both are compared in the same population. Brumfitt & Pursell (1972) and Kasanen *et al.* (1981) found that the difference in relapse rate between trimethoprim and cephalexin when they were randomly prescribed to patients from general practices, with microbiologically confirmed urinary tract infections, but without benefit of *in vitro* sensitivities of the infecting organism, was similar to that in the present study. Use of a 2 g total daily dose of cephalexin (Brumfitt & Pursell, 1972) did not reduce the relapse rate. The following explanations of the relative lack of efficacy of cephalexin have been proposed; development of spheroplasts which persist in a hyperosmotic or iso-osmotic environment (Gower & Tasker, 1976), filamentation of *Enterobacteriaceae* which reduces the bactericidal effect of the drug (Greenwood & O'Grady, 1976), and production, by *Enterobacteriaceae*, of amounts of β-lactamases too small to affect standard *in vitro* sensitivity testing (Brauner *et al.*, 1978).

Considerable co-operation is required from the patient if a 7 day antibacterial course is to be completed. Moreover, the more complex the daily dosage schedule is, the greater the difficult patients have in incorporating it into their daily routine (Cockburn *et al.*, 1987). Even under conditions of a clinical trial, nearly one-third of our patients given a twice daily schedule, and two-thirds of those on a four times daily one, failed to open their pill boxes sufficient times to complete the course. Where less attention is paid to the patient, compliance may be worse. Failure of therapy may lead to disillusionment and reduced compliance with a second conventional course or with the prolonged course of medication recommended (Fang *et al.*, 1979) for presumed renal parenchymal infections. It therefore appears sensible to reduce the amount of co-operation required with the first line treatment by using a short course or a single dose. Although a single 200 mg dose of trimethoprim had a cure rate of only 67% whilst 200 mg twice daily for 5 days cured 94% of urinary tract infections (Lacey *et al.*, 1981), a single dose of 400 mg was equally effective as a course of 200 mg twice daily for 7 days (Jones, 1983). In the case of cephalexin, a 3 day course in patients categorised as having lower urinary tract infections by the antibody coated bacteria test (Thomas *et al.*, 1974; Harding *et al.*, 1978) cured only 69%, a result similar to that found in those whose renal infections were treated for only 14 days (Preiksaitis *et al.*, 1981). The cure rate of single 3 g doses was age related (Cardenas *et al.*, 1986), ranging from 87% in 19 to 29 year olds to 42% in those aged 40 years or more. This may be the result of a higher incidence of renal infections and of lower urinary drug concentrations, as a consequence of the declining glomerular function. Thus although single doses of trimethoprim are a convenient first line treatment, it is advisable to use cephalexin in short or conventional courses in the middle aged and elderly. Like our own, these studies were performed in predominantly female populations. It is not known how applicable the results are to men. There is also the risk

that single doses may fail to eradicate any prostatic infection (Tolkoff & Rubin, 1983).

Estimating compliance with therapy is essential to any clinical trial where medication is self-administered. If compliance is poor, both adverse drug reactions and efficacy may be underestimated and over exacting regimens may become established. Like Evans & Spelman (1983), we found demographic details of little use in predicting non-compliance. Spot checks on the concentration of a drug, its metabolite or a marker, in blood or urine can show only that a dose has been taken within a period dependent on the elimination half-time of the compound, and their interpretation may be complicated by inter- and intra-individual variation in pharmacokinetic handling. Counting the number of tablets remaining in a container does not reveal when tablets were removed, and may, as in the present study, grossly overestimate the number which have been removed according to the prescribed pattern. If one assumes that if a medication container is accessed according to a recurrent pattern, its contents are being used, then remote monitoring of self medication habits, using a device coupled to the container, should resolve some of the difficulties encountered when assessing compliance (Moulding, 1979; Norell, 1983). Monitoring the use of a container does not, of course, guarantee that the patient has actually swallowed the medication.

The pill box described fulfilled the design objectives to produce a device which was small, suitable for a wide range of pills and capsules, and ease to use by the elderly and disabled. However, an obvious limitation of the system is that the number of openings can overestimate the number of occasions when medication is removed: the box was opened excessively in the first few hours after delivery, presumably as a result of the curiosity provoked in the patient and/or his friends and relatives. This discrepancy becomes small when the full 6 week capacity of the memory is used to monitor maintenance therapy.

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